SUMMARY OF COMMENTS FROM STERILE DRUG PRODUCTS AND DRUG SUBSTANCES BREAK OUT SECTIONS

MODERATORS: ANDREA HIGH, FDA — DAVID DESRIS, INDUSTRY
DAVID HUSSONG, FDA — RICHARD STEC, INDUSTRY

DATE: JUNE 11, 2001

RECOMMENDATIONS

1. SPECIFY FILING LEVELS (E.G., PAS, CBE, AR) FOR CHANGES TO CLEANING PROCEDURES AND STERILIZATION OF EQUIPMENT IN THE MANUFACTURE OF DRUG SUBSTANCE AND STERILE DRUG PRODUCT.

2. EXPAND THE SITE CHANGE CATEGORIES TO DIFFERENTIATE FILING LEVELS.

3. HOW BIG OF A CHANGE IN THE STERILIZER LOAD IS SIGNIFICANT? RECOMMEND CLARIFYING THE SIZE OF A LOAD CHANGE AND APPROPRIATE FILING LEVEL (PAS OR CBE).

4. RECOMMEND ADDING ACCEPTANCE CRITERIA FOR MEDIA FILL STUDIES TO HARMONIZE DATA REQUIREMENTS BETWEEN THE DISTRICT AND THE CENTER.

5. RECOMMEND CHANGES TO REDUCE THE FILTER PORE SIZE TO BE DOWNGRADED FROM A PAS.

6. RECOMMEND EXPANDING THE PACKAGING SECTION WITH REGARD TO CONTAINER CHANGES:

   A. CHANGE IN CONTAINER SHAPE AND SIZE – RECOMMEND MORE DETAIL TO PROVIDE FOR LOWER FILING CATEGORY. CHANGE IN CONTAINER SIZE/SHAPE REQUIRES A PAS. NOT QUANTIFIED AS TO HOW MUCH OF A CHANGE REQUIRES A FILING. RECOMMENDED THE USE OF PRE-APPROVED PROTOCOLS TO QUALIFY OR TO REDUCE FILING CATEGORY.

   B. CHANGE IN CONTAINER/CLOSURE (E.G., EFFECT OF HEADSPACE, SIZE, ETC) – SAME COMMENT AS IN 6.A.

   C. RECOMMEND INCORPORATING THE USE BRACKETING TO SUPPORT A LOWER FILING REQUIREMENT (CURRENTLY PAS) FOR INTRODUCTION OF INTERMEDIATE PACKAGING SIZES. (E.G., 1 ML IN A 2 ML FILL AND 20 ML FILL CONTAINERS ARE APPROVED, USE BRACKETING APPROACH TO FILE 10ML FILL IN A 20 ML).

7. REDUCE REGULATORY BURDEN (I.E. DATA REQUIREMENTS AT THE TIME OF FILING) ON POST APPROVAL CHANGE BASED ON:
   - FIRM'S PAST SUBMISSION HISTORY
   - USE OF NEW TECHNOLOGY
   - FIRM'S INSPECTION HISTORY
   - DATA PACKAGE SUBMITTED IN THE ORIGINAL APPLICATION

8. RECOMMEND ADDING TO GUIDANCE INSTRUCTIONS ON HOW TO REFERENCE PREVIOUSLY SUBMITTED INFORMATION TO ALLOW FOR DEREGULATION OF SUBSEQUENT SUBMISSIONS.

9. ISSUE SEPARATE GUIDANCE FOR SUITABILITY FOR ASEPTIC PROCESSING VERSUS T.S.

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10. GUIDANCE SECTION VI.B.4: A CHANGE TO A CONTRACT STERILIZATION SITE FOR PACKAGING COMPONENTS CAN BE FILED IN AN ANNUAL REPORT IF THE PROCESSES ARE NOT "MATERIALLY DIFFERENT". IF SAMENESS CAN NOT BE ASSESSED, THE FILING REQUIREMENT MOST LIKELY BECOMES PAS (GUIDANCE DOES NOT SPECIFY, JUST AN INTERPRETATION). RECOMMEND REDEFINING "MATERIALLY DIFFERENT" AND ALLOW FOR A LESSOR FILING REQUIREMENT IF SAMENESS CAN NOT BE CONFIRMED.

11. RECOMMEND ADDING TO THE GUIDANCE THE FILING REQUIREMENTS FOR:
    - TO ADD NEW CONTAINER WITH NEW DIMENSIONS
    - TO ADD A NEW OR DIFFERENT VENDOR FOR A CONTAINER OF THE SAME SIZE

GENERAL COMMENTS AND QUESTIONS

1. DOES THE AGENCY VIEW THE FILING CATEGORIES THE SAME/DIFFERENT FOR STERILE AND NON-STERILE DRUG SUBSTANCES.

2. REQUESTING PROVISION TO ACCELERATE THE REVIEW OF DMFS CONTAINING STERILITY ASSURANCE DATA.

3. INSTALLED A NEW FILL LINE IN A DIFFERENT MANUFACTURING SUITE. FILL LINE WAS THE SAME AS EXISTING LINES. FILED A CBE BUT AGENCY UPGRADED SUBMISSION TO A PAS – WHY?

4. NO GUIDANCE ON STOPPER CHANGES FROM ONE FORMULATION TO ANOTHER

5. ENCOURAGE THE FILING OF PROCESS IMPROVEMENTS BY LOWERING FILING REQUIREMENTS TO MAKE GOOD CHANGES (MODERNIZATION).

6. WIDE DISPARITY IN REVIEW CYCLES BETWEEN OGD AND ONDC INHIBITS ABILITY TO IMPLEMENT CHANGES SIMULTANEOUSLY FOR MULTIPLE PRODUCTS FROM THE SAME FACILITY.

7. CONSIDER PRIOR APPROVAL IN 60 DAYS – NEW CATEGORY

8. GUIDANCE ON HOW OLD INFORMATION IN AN APPLICATION CAN BE REFERENCED FOR NEW SUPPLEMENTS.

9. DIFFERENT IN PACSAS AND 1999 GUIDANCE FOR REGULATORY CHANGES: PACSAS PROVIDED MORE INFORMATION ON DATA PACKAGE TO FILE CHANGE

10. GUIDANCED PUBLISHED BY COMPLIANCE MAY BE IN CONFLICT WITH REVIEW DISCIPLINE.

11. WILL FDA ENFORCE USP MONOGRAPHS? USP AND FDA NEED TO COLLABORATE TO A GREATER EXTENT (E.G., MICROBIAL ATTRIBUTES).

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12. THERE IS CONCERN THAT PACSAS INFORMATION WILL NOW BE IN TWO GUIDANCE (CHANGES GUIDANCE AND REVISION OF 1994 STERILIZATION VALIDATION GUIDANCE).

13. GUIDANCE SOUGHT TO VALIDATE LARGER BATCHES (I.E., MORE THAN 24 HOURS, 7-DAYS SHOULD BE ACCEPTABLE).

14. WHAT IS THE DEFINITION OF "POTENTIAL"?

15. HOW TO PROPERLY VALIDATE STERILIZATION OF STOPPERS – IS IT NECESSARY TO INOCULATE THE STOPPERS DIRECTLY WITH A BIOLOGICAL INDICATOR?

MISCELLANEOUS POINTS

1. JOINT INSPECTIONS BETWEEN REVIEWER AND INSPECTOR

2. VIII.B.5 PAS FOR CHANGES TO ANALYTICAL PROCEDURES FOR PACKAGING COMPONENTS (VERY GENERAL CLASSIFICATION) IS TOO RESTRICTIVE

3. ESTIMATE TIME FOR UPDATING THE 1994 STERILITY VALIDATION GUIDANCE ?

4. COVER LETTERS FOR CBES SHOULD INCLUDE A RATIONALE AS TO WHY THE SUBMISSION QUALIFIES AS SUCH. SHOULD BE MORE THAT JUST A REFERENCE TO THE APPROPRIATE SECTION OF THE GUIDANCE.

5. IF STARTING MATERIAL IS 3 STEPS PRIOR TO THE API FOR A NATURAL PRODUCT BUT THE SYNTHESIS IS ONE STEP, HOW DO WE DEFINE STARTING MATERIAL?

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